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May 24, 2008.



To : Dr. Yelena G. Gakh
US patent & Trademark Office
PO Box 1450
Alexandria, VA 22313-1450

Re : Application No. 10/675,764
Art Unit 1743

Dear Dr. Yelena G. Gakh :

We, the applicants, kindly ask your permission to chronologically reply to the office action on 04-24-2008 as follows :

1. Response to Amendment

The previous amendment was not meant to introduce new matter but rather to "rephrase" the subject matter. However, because the office regarded this amendment as introducing new matter, we request that the amended materials be removed. The "Background of The Invention", the "Brief Summary of The Invention", and the "Detailed Description of The Invention" are currently amended to delete the amended materials. Added text are underlined and deleted text are strike through in brackets.

The "Brief Description of The Drawings" is also amended by removal of 4 mass spectra, leaving one representative mass spectrum of the synthesized internal standard as requested.

2. Information Disclosure Statement

The "List of References" and the "Abstract of The Disclosure" are the original sections of the specification.

3. Claim Objections

We ask that claim 26 be canceled.

Claim 27 is amended to limit the carboxylic acids in claim 25 to small molecular weight carboxylic acids (less than 1000 atomic mass unit). The size of the R1 group is limited to the above molecular weight.

Claim 28 is amended to limit the labeled carboxylic acid ester to small molecular weight carboxylic acid ester (less than 1000 atomic mass unit). The size of the R1 and R2 groups are limited to the above molecular weight.

4. Claim Rejections

The invention provides a method of synthesis of labeled internal standard for the purpose of identification and quantification of carboxylic acid in a sample that is of "known" chemical structure but of "unknown" concentration. The method cannot be applied to the identification and quantification of an "unknown" carboxylic acid. The instrument for this analysis is a mass spectrometer which measures the responses as

intensity of specific masses. The carboxylic acids to be identified and quantified have to be of "known" chemical structures so that their characteristic masses can be measured. We are sorry if we mislead the office to the confusion of "unknown" carboxylic acid. The phrase "unknown carboxylic acid" was not used in the specification and the claims. The provided example is the analysis of ketoprofen in human plasma. Chemical structure of Ketoprofen is known, so its molecular mass can be calculated and its molecular mass ion can be input into the mass spectrometer for measurement. The concentration of Ketoprofen in samples to construct a calibration curve is known (samples A to G), but the concentration of Ketoprofen in patient sample is "unknown" and can be deduced from the calibration curve.

It is known in this art that stable isotope labeled internal standard for the analysis of a carboxylic acid is a chemical that has the same chemical structure as that of the carboxylic acid except that a few of its atoms are replaced by a stable isotope atoms (deuterium, carbon-13, nitrogen-15, etc.). It is a "labeled carboxylic acid". This internal standard is often synthesized from an authentic sample of the carboxylic acid by often lengthy organic synthesis methods. This invention provides a one step synthesis of a stable isotope labeled chemical that can be used as labeled internal standard from an authentic sample of the carboxylic acid. The difference between this invention and prior art is that the labeled internal standard of this invention is not a labeled carboxylic acid. It is a "labeled carboxylic acid ester". Therefore the carboxylic acid in the sample has to be derivatized to the same but non-labeled ester before mass spectrometry analysis. We ask that the phrase "additional chemical reaction" in claim 25 be replaced by "the derivatizing reaction" to clarify the method.

Because the labeled internal standard ester is already derivatized, it "cannot" react with the non-labeled derivatizing reagent that derivatizes the carboxylic acid. The non-reactivity of the labeled internal standard ester is not a condition for derivatizing the carboxylic acid. So for clarity purpose, we ask that the phrase "and wherein there is no reaction of said labeled carboxylic acid ester with said derivatizing reagent" in claim 25 c) be deleted to avoid confusion.

We also ask to amend claim 39 to show that all carboxylic acids in the sample are derivatized simultaneously by one derivatizing reagent. We ask to amend claim 40 to show that all labeled carboxylic acid esters are synthesized simultaneously by one labeled derivatizing reagent. Claim 44 is asked to be canceled. We ask to amend claim 45 in proper format. The claim listing is submitted in a separate sheet.

Kind regards,



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